Multiple Electrophilic Substitution of 1,1,2,2,9,9,10,10-Octafluoro[2.2]paracyclophane

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Synthetic methods for introduction of two substituents into the rings of octafluoroparacyclophane are presented. Nitration gives three isomers with nitro substituents on different rings: pseudo-ortho, pseudo-meta, and pseudo-para, in equal amounts. These dinitro compounds are shown to be precursors of a variety of other disubstituted OFP derivatives. Methods of characterization of isomeric disubstituted OFPs are extensively discussed, and the ^{1}H and ^{19}F NMR spectra of these derivatives are analyzed explicitly.

Introduction

[2.2] Paracyclophane ([2.2] PCP) chemistry has grown considerably since the isolation of the parent compound in 1949.[1] Besides finding commercial application as monomers for parylene-type polymers,[2] these attractive molecules have spawned an unusual and unique chemistry.[3] The close proximity of the face to face aromatic rings, coupled with the rigid skeleton and high strain energy[4] translates into such effects as transannular interactions, thermal racemization and isomerism, surprising directing effects in multiple electrophilic substitution and unusual spectroscopic phenomena.[3] The use of ring-substituted [2.2] PCP skeletons as chiral backbones is of considerable current interest.[5] Highly fluorinated cyclophanes on the other hand, have received much less attention, even though these compounds have desirable industrial properties[6] and should at least display as equally rich a chemistry as their hydrocarbon counterparts. This imbalance is slowly being redressed following the improved syntheses of the bridge fluorinated cycle 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane (OFP) **1** that have been reported over the last 7 years[7−10] and our initial report of the chemistry of this fluorinated cyclophane.[11]

Here we wish to report the synthesis, characterization and thermal isomerization of a variety of both homo- and heteroannularly disubstituted OFP derivatives. Prior to this paper, there were no reports of disubstituted OFP derivatives in the literature.[12]

Synthetic Results and Discussion

Recently we reported that nitration of **1** gave a mononitro product in high yield.[11] However, when such nitration is carried out under the more forcing conditions of 5 equiv of NO_2BF_4 and a temperature of 80 °C, the products generated were observed to be a mixture of three isomeric dinitro derivatives in over 80% combined isolated yield., with the ratio of the isomers being 1:1:1 [Scheme 1].

One of the isomers could be separated from the other two by column chromatography since it displayed a lower R_f value than the other two, which coeluted. The quicker running mixture of two isomers could be enriched in one or the other isomer by fractional crystallization or sublimation. The ^{19}F NMR spectrum of each isomer showed only two AB patterns. (Recall that the ^{19}F NMR spectra of OFP consists of a singlet, and that mononitro-OFP appears as four AB patterns).[11] The increase in the symmetry of these new products relative to mononitro-OFP indicated incorporation of at least two nitro groups.

Mass spectrometry confirmed not only that the products did indeed contain two nitro groups but also that they were located on different rings. The relative orientation of the nitro groups in each of the three isomers was established through ^{1}H NMR and further confirmed by thermal isomerizations and correlation of their physical properties with those already established for heteroan-

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(2) Gorham, W. F. *J. Polym. Sci. Part A-1* **1966**, *4*, 3027.
(3) Reviews: (a) Vogtle, F. *Cyclophane Chemistry*; Wiley: New York, 1993. (b) Boekelheide, V. *Top. Curr. Chem.* **1983**, *113*, 87. (c) Hopf, H.; Marquard, C. *Strain and Its Implications In Organic Chemistry*; Kulwer: Dordrecht, 1989.
(4) Hope, H.; Bernstein, J.; Trueblood, K. N. *Acta Crystallogr., Sect. B* **1972**, *28*, 1733.
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(6) (a) Beach, W. F.; Lee, C.; Basset, D. R.; Austin, T. M.; Olson, A. R. Xylylene Polymers. In *Wiley Encyclopaedia of Polymer Science and Technology*; Wiley: New York, 1989; Vol. 17, p 990. (b) Majid, N.; Dabral, S.; McDonald, J. F. *J. Electron. Mater.* **1989**, *18*, 301. (c) Williams, K. R. *J. Thermal Anal.* **1997**, *49*, 589.
(7) Dolbier, W. R., Jr.; Asghar, M. A.; Pan, H.-Q.; Celewicz, L. *J. Org. Chem.* **1993**, *58*, 1827.
(8) Dolbier, W. R., Jr.; Rong, X. X.; Xu, Y. *J. Org. Chem.* **1997**, *62*, 7500.
(9) Dolbier, W. R., Jr.; Duan, J.-X.; Roche, A. J. U.S. Patent 5,841,-005, 1998.
(10) Dolbier, W. R., Jr.; Duan, J.-X.; Roche, A. J. *Org. Lett.* **2000**, *2*, 1867−1869.
(11) Roche, A. J.; Dolbier, W. R., Jr. *J. Org. Chem.* **1999**, *64*, 9137.
(12) Bromination of OFP was reported in these two patents. The products were ill-characterized, and in our hands, the reaction was unable to be reproduced. (a) Marvel, C. S. U.S. Patent 4,499,258, 1985 (b) Marvel, C. S. U.S. Patent 4,476,062, 1984.

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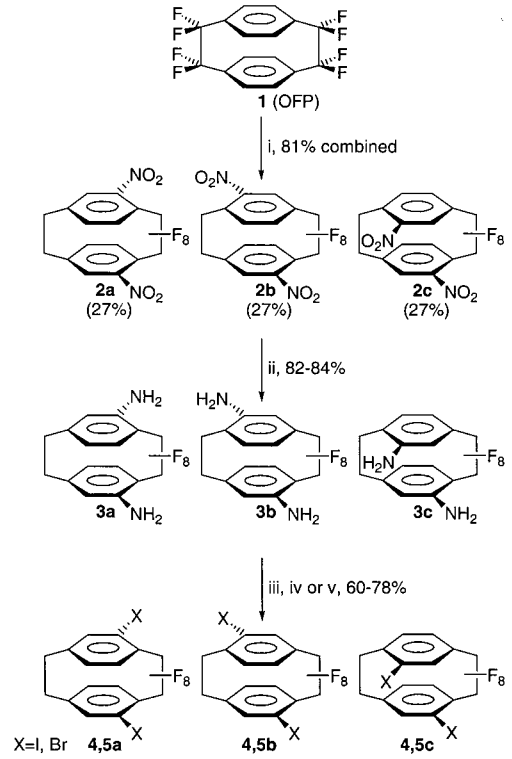
Scheme 1. Syntheses of Dinitro-, Dibromo-, and Diiodo AF4 Derivatives



Reagents and conditions:
i: 5 equiv. NO_2BF_4, Sulpholane, 80°C 16hrs
ii: Fe, HCl, EtOH/H_2O, Reflux, 4hrs
iii: H_2SO_4, H_2O, $NaNO_2$, CH_3CO_2H, 0-5°C, 2hrs
iv: CuBr, HBr, 70°C, 2hrs
v: KI, H_2O, 70°C, 2hrs.

nularly disubstituted [2.2] PCP derivatives. (More detailed explanations of these characterizations are provided later). Thus the products were identified as pseudo-*m*-, pseudo-*p*-, and pseudo-*o*-dinitrooctafluoroparacyclophanes **2a**−**c**. No evidence of the pseudo-geminal isomer was observed, although as little as 1% could have been detected.

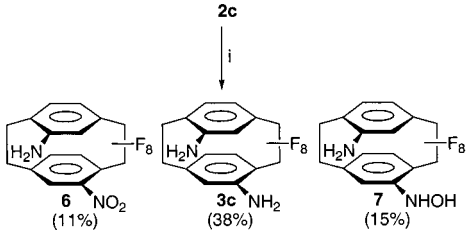
Obviously the introduction of a nitro functionality into one ring deactivates that ring to further electrophilic substitution and guides subsequent reaction to the other unsubstituted ring. The lack of a pseudo-geminal isomer is somewhat surprising since there are many examples of complete (or predominant) pseudo-geminal electrophilic aromatic substitutions promoted by substituents bearing basic functionalities, through their participation as intramolecular bases.[3] However, nitrations are known to be less susceptible to such kinetic effects, in comparison to brominations, for example.[11] We propose that the lack of such a dinitro isomer in this reaction is due to a steric effect. (The nitration of the hydrocarbon [2.2] PCP using nitric acid at 75 °C is reported[14] to yield mononitro [2.2] PCP (26%), and pseudo-meta (2%), pseudo-para (2%), pseudo-ortho (1.4%) and pseudo-geminal (0.7%) dinitro isomers).

We have previously demonstrated that nitro-OFP provides a route to a variety of ring-substituted OFP derivatives,[11] and thus we were able to apply similar synthetic methodology that allowed the generation of a number of interannularly disubstituted OFP products.

(13) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3505.
(14) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3527.

It is noteworthy that the reactions in Scheme 1 were all performed on both single isomers and mixtures of the three isomers. The pseudo-ortho isomer could always be separated from the pseudo-meta/pseudo-para mixture by column chromatography, regardless of the substituents. The pseudo-meta/pseudo-para isomers were, in general, unable to be separated by column chromatography. Monosubstituted and unsubstituted OFP contaminants arising from reduction processes could always be removed from disubstituted products by column chromatography. All reaction yields were essentially the same whether performed on single or multiple isomers, and they are comparable to the corresponding reactions used to make the monosubstituted OFP analogues.[11] The only difference in reactivity for the three disubstituted isomers in the reactions in Scheme 1 was observed in their trifluoromethylation reactions, where the pseudo-ortho diiodo isomer gave lower conversions and slower reactions. This anomaly is addressed later in the text. No isomerism or loss of integrity of the OFP skeleton was observed during any of these reactions, although the deliberate high temperature thermal isomerization of selected examples of these compounds was studied.

The reduction of **2a**−**c** using iron powder/concentrated hydrochloric acid gave the corresponding diamino products **3a**−**c** in good isolated yields (82−84%). Cyclophanes containing electron donating substituents in one ring and electron acceptors in the other ring are often reported to be colored, and the corresponding interannular nitro/amino systems for the hydrocarbon [2.2] PCP vary from yellow to red, depending on the relative orientation of the two substituents.[3,15] In an attempt to generate **6** with an amino group in one ring and a nitro in the other, the milder reducing agent of cyclohexene and Pd on carbon was used in conjunction with **2c**. Besides the corresponding diamino OFP **3c** (38%), we were able to isolate the nitro-amino derivative **6** (11%), and the hydroxylamino-amino product **7** (15%).



Reagents and conditions, i: Cyclohexane, Pd/C, EtOH, Reflux, 15mins.

Disappointingly, **6** was a white solid, in contrast to the orange/yellow color of the corresponding [2.2] PCP compound.[15] This difference can be attributed to removal of electron density from the interacting π systems by the electron-withdrawing fluoroalkyl bridging units,[16] thus reducing charge transfer.

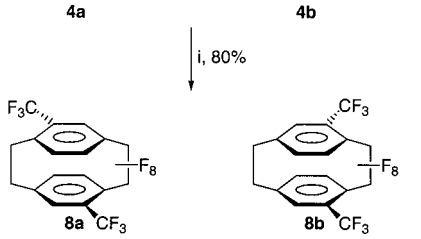
The diamino OFP isomers **3a**−**c** proved versatile starting materials for further transformations, with the most straightforward being the formation of the respective *N*-acetyl- and -trifluoroacetyl-amides in high isolated yield (84−97%). These compounds proved useful not only for characterization purposes but also as protecting

(15) Allgeier, H.; Siegel, M. G.; Helgeson, R. C.; Schmidt, E.; Cram, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 3782.
(16) Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, 1973.

groups that moderated the reactivity of the diamino OFP systems and thus made appropriate materials for the high temperature thermal isomerization studies described later.

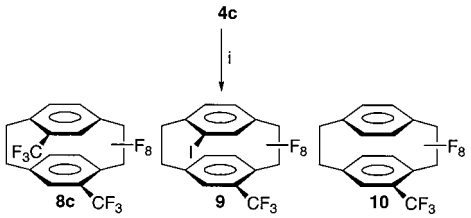
The double diazotization of these diamino-systems proved as successful as diazotization of monoamino-OFP,[11] and thus the three isomeric dibromo- (**5a**−**c**) and diiodo-OFP (**4a**−**c**) derivatives were prepared in good isolated yield (60−78%) via Sandmeyer-type chemistry. The heteroannular dibromides proved useful for comparison purposes when we later prepared a homoannular dibromide (vide infra), and they also served as useful intermediates for further transformations, although the diiodides generally gave higher yields in such reactions and were therefore the more desirable starting materials.

Trifluoromethylation[17] of the pseudo-meta and pseudo-para OFP diiodides **4a**,**b** gave moderate yields of corresponding bis(trifluoromethylated) products **8a**,**b** (50%), along with appreciable amounts monotrifluoromethylated **10** (30%). This is in keeping with our previous experience regarding the trifluoromethylation of iodo-OFP,[11] and more importantly, it was again observed that the addition of a catalytic amount of palladium dichloride gave vast improvements in the yields of bis(trifluoromethylated) products (80%), and a consequent decrease in chemically reduced side products.



Reagents and conditions
i: $FSO_2CF_2CO_2CH_3$, CuBr, $PdCl_2$, DMF, 80°C, 16hrs

When a typical uncatalyzed trifluoromethylation was performed on pseudo-ortho OFP diiodide **4c**, the only two products obtained besides starting material were identified as **10** (33%) and pseudo-ortho iodo-trifluoromethyl OFP **9** (21%). However, addition of $PdCl_2$ promoted a superior reaction with the pseudo-ortho bis(trifluoromethyl) derivative, **8c**, being isolated in 68% yield, along with a 10% yield of iodo-trifluoromethyl derivative, **9**, which could itself be reduced by zinc in acetic acid to form trifluoromethyl-OFP (91%).



Reagents and conditions
i: $FSO_2CF_2CO_2CH_3$, CuBr, ($PdCl_2$), DMF, 80°C, 16hrs

The difference in reactivity displayed by the isomeric diiodides can be best understood in terms of the iodides simply being located either on the same or different sides of the cyclophane. Although exchange of trifluoromethyl for iodine should make the iodo-trifluoromethyl intermediate compounds more reactive toward further substitution, clearly this is not the case for the pseudo-ortho isomer. It is likely that the two reaction centers in the pseudo-ortho isomers are so close[4] that when one iodine is replaced by a trifluoromethyl group, there is sufficient steric and electronic shielding by the attached trifluoromethyl group to inhibit further substitution. Having observed through space NMR interactions between syn bridging fluorines and a trifluoromethyl substituent on the ring,[11] we believe that these syn bridge fluorines also provide steric and electrostatic shielding to an attacking nucleophile. The use of a relatively large transition metal catalyst like Pd(II) may serve to reduce such steric constraints on the incoming nucleophile by coordinating the substrate and the nucleophile before joining them through a reductive elimination,[18] thus resulting in the superior observed yields of trifluoromethylated products in $PdCl_2$ catalyzed reactions.

The pseudo-ortho diiodide **4c** was also used to produce the corresponding diphenyl derivative via reaction with phenylmagnesium bromide and $PdCl_2$, providing the diphenyl derivative, **11**, in 21% yield along with 20% monophenyl-OFP, **12**. Identical mono and diphenylated products were also obtained via diazonium chemistry and benzene.

Although the overall yields of the diiodides and dibromides were acceptable for a three-step procedure (40−53% isolated yield from OFP), a *direct* bromination procedure to dibrominate OFP would be much more desirable. To this end, OFP was subjected to several literature bromination methods,[9,19] but the only method that was successful in generating more than a trace of dibromo-OFP was a method recently reported from this laboratory for bromination of deactivated aromatics.[20]

When a trifluoroacetic acid solution of OFP was exposed to a combination of four equivalents of NBS and sulfuric acid at 80 °C, a single major product was produced. The presence of two AB patterns in the ^{19}F NMR of this compound led us to believe it was a dibromide product. The isolated yield of this compound, after column chromatography, was 55%, and somewhat surprisingly, the NMR spectra of the product did not match any of those of the three interannular dibromides that had been prepared via the nitration/reduction/diazonium chemistry described earlier. Mass spectrometry revealed that the product was indeed a dibromide isomer, but that the bromines were both on the *same* ring. This information, coupled with the ^1H and ^{19}F NMR patterns (see discussion later) indicated that this was *p*-dibromo OFP **5d**.

A bromine substituent is normally viewed as a deactivating and ortho/para directing substituent in electrophilic aromatic substitution.[21] Usually a deactivating substituent would guide subsequent substitution into the

(17) Chen, Q.-Y.; Wu, S.-W. *J. Chem. Soc., Chem. Commun.* **1989**, 705

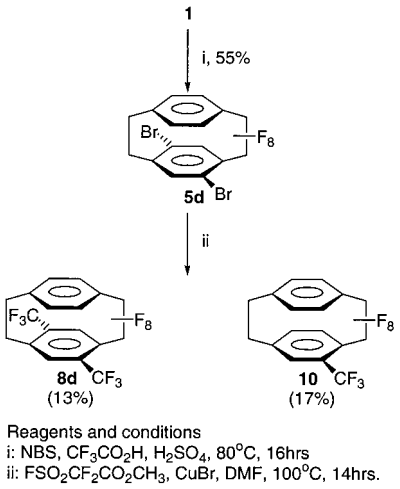
(18) Rozenberg, V. I.; Sergeeva, E. V.; Kharitonov, V. G.; Vorontsova, N. V.; Vorontsov, E. V.; Mikul'shina, V. V. *Russ. Chem. Bull.* **1994**, *43*, 1018.

(19) (a) Kodaira, K.; Okuhara, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1625. (b) Mongin, F.; Maggi, R.; Schlosser, M. *Chimia* **1996**, *50*, 650. (c) Porwisiak, J.; Schlosser, M. *Chem. Ber.* **1996**, *129*, 233.

(20) Duan, J.-X.; Zhang, L.-H.; Dolbier, W. R., Jr. *Synlett.* **1999**, 1245.

(21) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed., Part A; Plenum Press: New York, 1990; Chapter 10.

other ring of a [2.2] PCP,[13] but this was obviously not the case for this reaction, although the second bromine did enter para to the first. (When [2.2] PCP was dibrominated using Fe/Br_2, the product ratio was para (5%), pseudo-ortho (16%), pseudo-para (26%) and pseudo-meta (6%).)[13]



With *p*-dibromo OFP (**5d**) in hand, it was then possible to prepare the *p*-bis(trifluoromethyl) OFP derivative, **8d**, albeit in lower yields than had been obtained for the heteroannular diiodides. As expected, the NMR spectra of **8d** were also distinctively different from those of **8a**, **b**, and **c**.

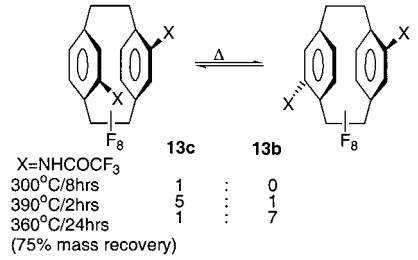
Synthetic Conclusions. Two complementary methods for the introduction of two substituents into the rings of octafluoroparacyclophane have been reported. Nitration gives three isomers with the nitro functionalities in different rings, oriented pseudo-meta, pseudo-para and pseudo-ortho. Bromination on the other hand gives a dibromide where both halogens are in the same ring, para to each other. All such products serve as versatile starting materials for preparation of a variety of novel homo- and heteroannular disubstituted OFP derivatives.

Thermal Isomerizations

The [2.2] PCP skeleton is rigid[4] and under normal conditions maintains its integrity, allowing, for example, the application of [2.2] PCP derivatives as chiral ligands and molecular scaffolds of known fixed geometry.[5] This holds true for temperatures below 150−200 °C. Above these temperatures, ring substituted [2.2] PCP derivatives exhibit a thermal isomerization that is unique to this system. Typically, the deliberate isomerizations have been performed without solvent at 200 °C for 24 h, and Cram elegantly demonstrated that they proceeded though a bibenzyl-type diradical intermediate.[22]

One might expect the longer C−C bridge length in OFP (1.577 Å) relative to [2.2] PCP (1.569 Å)[4] to allow the racemization of OFP derivatives to occur at lower temperatures since it is this bond that must break and reform. Conversely, since replacement of hydrogen by fluorine in saturated systems usually increases thermal and chemical stability,[16] coupled with the lower stability of difluorobenzyl radicals relative to benzyl radicals,[23] OFP derivatives might be predicted to require much higher temperatures to undergo such isomerizations. We were therefore interested to determine whether OFP derivatives would undergo such thermal isomerizations, and if so, what temperatures would be required.

Initially the pseudo-ortho dibromo-, pseudo-ortho diamino- and dinitro-OFP derivatives were examined, but these compounds proved to be perfectly stable and unchanged when heated neat at 200 °C for 12 h. After 8 h at 300 °C, the diamino compound had fully decomposed, while the dibromo and dinitro compounds showed no isomerization. When the temperature was raised to 350 °C the dinitro compound was extensively charred but showed traces of isomerization to its pseudo-para counterpart, whereas the dibromide was also charred but showed no isomerizations. In contrast, heating the pseudo-ortho bis(trifluoroacetamido) OFP, **13c**, led to no charring, and the sample showed traces of isomerization to its pseudo-para isomer, **13b**. Therefore **13c** was heated to 381−390 °C for 2 h, and was shown by NMR analysis to have been converted to a 5:1 ratio of pseudo-ortho and pseudo-para isomers. Encouraged by this result, this



mixture was further heated at 350−360 °C for 24 h and the ratio of isomers was found to have changed to 1:7 in favor of the less sterically congested pseudo-para isomer. The mass recovery was 75%, with the balance presumably being insoluble polymeric material. Therefore the bridging fluorine atoms in OFP appear to impart 150 °C more kinetic thermal stability to a [2.2] PCP ring system. This not only demonstrates the stabilizing effect of exchanging fluorine for hydrogen, but has serious implications in the use of these fluorinated phanes as chiral ligands, catalysts and auxiliaries, since they display far superior resistance to thermal isomerization than the hydrocarbon analogues, and could therefore be employed at higher temperatures without losing their chirality through thermal racemization. (The observed isomerizations were also useful as they helped to further confirm the correctness of our isomer assignments).

Characterization

The introduction of a second substituent onto a ring in a [2.2] PCP system can give rise to seven possible isomers, of which three are racemic and four are meso (if the two substituents are equivalent). Therefore structure elucidation and perhaps more importantly, one's ability to distinguish isomeric products, is fundamental to meaningful work in this field. For this reason, there has been substantial work in this area,[15,24,25] and numerous strategies and techniques have evolved that allow unambiguous isomer and structure determination in hydrocarbon [2.2] PCP systems, with ^{1}H NMR and mass

(22) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3517.
(23) Dolbier, W. R., Jr. *Chem. Rev.* **1996**, *96*, 1557.
(24) Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3534.
(25) Ernst, L. *Liebigs Ann.* **1995**, 13.

Table 1. Amino OFP SCS Values[a]

o	m	p	*m′*	*p′*	*o′*	gem
−1.21	0.36	−0.76	−0.20	0.01	−0.12	+0.69

[a] Where *o* = ortho, *p* = para, *m* = meta, *m′* = pseudo-meta, *p′* = pseudo-para, *o′* = pseudo-ortho and *gem* = pseudo-geminal.

Table 2. Predicted ^{1}H Chemical Shifts Using Amino OFP SCS Values

compound	peak type	SCS effects	calcd (ppm)	obsd (ppm)
pseudo-meta diNH$_2$ **3a**	singlet	*o* + *p′*	6.10	6.08
	A	*m* + *gem*	7.63	7.57
	B	*p* + *o′*	6.42	6.44
pseudo-para diNH$_2$ **3b**	singlet	*o* + *m′*	5.89	6.00
	A	*m* + *o′*	6.82	6.87
	B	*p* + *gem*	7.23	7.04
pseudo-ortho diNH$_2$ **3c**	singlet	*o* + *gem*	6.78	6.89
	A	*m* + *p′*	6.95	7.00
	B	*p* + *m′*	6.34	6.36

spectrometry comprising the most powerful tools. Previously we reported that not only were these strategies and techniques equally applicable to the characterization of mono substituted OFP derivatives, but that the OFP derivatives also offered the added bonus of ^{19}F NMR to distinguish between products.[11] In the following section we will demonstrate that the ^{1}H Substituent Chemical Shift (SCS) values previously derived for the amino-OFP system[11] allow accurate prediction of the ^{1}H shifts of the three new diamino-OFP products synthesized in this paper and also that the ^{19}F NMR shifts of the bis-(trifluoromethylated) OFP compounds (both hetero- and homoannular) can also be predicted via the use of the ^{19}F SCS values derived from monotrifluoromethylated OFP.

We believe that this is the first report of the calculation of ^{19}F SCS values, and the first demonstration that they may be used to predict the shifts of the bridging fluorines in multiply substituted OFP derivatives.

^{1}H NMR. As a result of their symmetric nature, heteroannularly identically disubstituted [2.2] PCPs display a simple and characteristic ^{1}H NMR pattern consisting of one singlet and one AB pattern. All of the disubstituted OFP products described herein also display this feature. The pseudo-ortho disubstituted isomer is generally the easiest to recognize since any "gem shift" operates upon the resonance which is a singlet, forcing it downfield, normally clear of the other resonances.

Since it has been demonstrated that amino substituted [2.2] PCPs are the most convenient for NMR investigation,[15] we earlier derived the SCS values for the amino-OFP system (Table 1). Prior work in hydrocarbon [2.2] PCP systems has amply shown that these SCS values are additive and therefore may be used to calculate proton shifts for multiply substituted systems. We can now compare the observed ^{1}H shifts for our three diamino-OFP isomers, with those shifts calculated from our SCS values (Table 2).

It is clear that there is good agreement between the predicted and observed chemical shifts. This is taken as further confirmation that not only were we accurate in our previous assignment of the amino-OFP resonances, but also our isomer assignments of the disubstituted products were also correct. In future work we aim to acquire SCS values for all of the monosubstituted OFP derivatives, and also demonstrate their ability to accurately predict ^{1}H NMR spectra of appropriately disubstituted OFP derivatives.

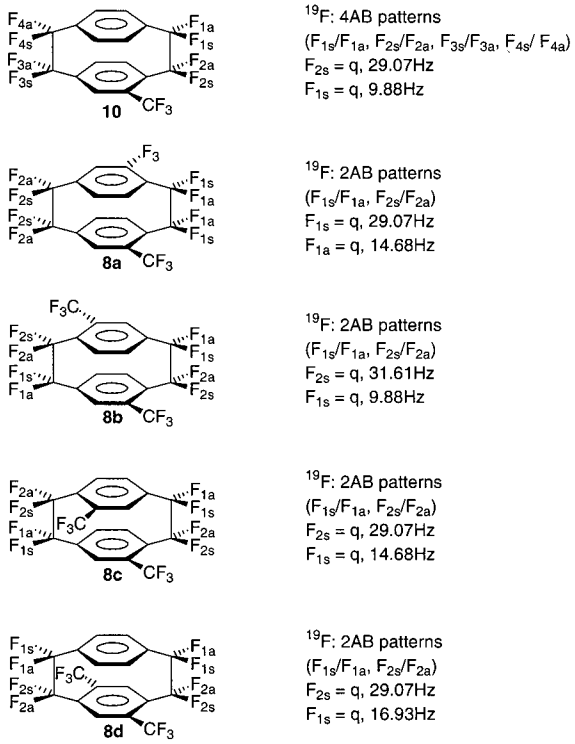


Figure 1. Assignment of bridge fluorine resonances in trifluoromethyl-substituted OFPs **10** and **8a**−**d**.

^{19}F NMR. Monofunctionalized OFP derivatives exhibit a characteristic four AB pattern in their ^{19}F NMR spectra,[11] whereas interannular identically disubstituted OFP derivatives contain only four different bridging fluorine atoms, which manifest themselves as two AB patterns. (This is also true for para and ortho oriented intraannular substituted OFP derivatives). All of the disubstituted OFP derivatives described herein display only two AB patterns in their ^{19}F NMR spectra. (Of course, OFP derivatives bearing two different substituents have eight different bridge fluorines that appear as four ABs, similar to a mono OFP product).

The problem previously described concerning the assignment of fluorine resonances to specific fluorine atoms still exists for the derivatives described here except for the four bis(trifluoromethyl)-OFP derivatives. The "through space" coupling that occurs between a trifluoromethyl ring substituent and the proximate syn bridging fluorines[11] allowed the instant recognition of those bridge fluorines since they appear as quartets. Their partners in the respective AB patterns could be located by line shape and coupling constants. Thus F_{1s}/F_{1a}, F_{2s}/F_{2a} for trifluoromethyl-OFP could be assigned, although the assignment of the remaining four fluorines was ambiguous.

However, because of symmetry in the bis(trifluoromethyl)-OFP derivatives **8a**−**d**, we can use this coupling interaction to fully assign, for the first time, the bridge fluorine resonances of these systems (and further confirm the accuracy of our isomer assignments) (Figure 1). The strategy was to first identify the resonances split into the large and small quartets and then find their AB partners. Easiest to identify was the pseudo-meta isomer, since this is the only isomer to contain both quartet

Table 3. ^{19}F SCS Values for 10 (ppm)

F_{1a}	F_{1s}	F_{2a}	F_{2s}	F_{3a}	F_{3s}	F_{4a}	F_{4s}
3.18	4.19	9.77	4.72	3.32	−0.19	2.55	0.38

Table 4. Calculated ^{19}F Chemical Shifts for 10, 8a−d

isomer	assignment	calculated	found
pseudo-para **8b**	F_{2s}	−110.73	−112.90
	F_{2a}	−107.85	−108.28
	F_{1s}	−110.49	−111.77
	F_{1a}	−115.01	−115.65
pseudo-meta **8a**	F_{1s}	−110.10	−112.03
	F_{1a}	−104.04	−105.86
	F_{2s}	−115.64	−118.29
	F_{2a}	−114.30	−113.56
pseudo-ortho **8c**	F_{2s}	−112.90	−112.23
	F_{2a}	−105.68	−108.07
	F_{1s}	−114.00	−114.75
	F_{1a}	−111.50	−113.16
para **8d**	F_{2s}	−109.96	−112.85
	F_{2a}	−108.42	−109.27
	F_{1s}	−111.26	−114.83
	F_{1a}	−114.44	−113.47

resonances within the same AB. (This also has the unfortunate consequence that the other two fluorines for this isomer cannot be assigned unambiguously). For the other isomers, the resonances with the larger and smaller quartets were assigned F_{2s} and F_{1s} respectively. Identification of their AB partners via line shape and coupling constant gave F_{2a} and F_{1a}. Thus, for the first time, all the fluorine atoms could be assigned to their fluorine resonances.

This presented a situation where we had ^{19}F chemical shifts and assignments for four disubstituted OFP derivatives and assignments for half of the shifts for the corresponding monosubstituted derivative. Since we have demonstrated that ^{1}H SCS values are additive for the OFP system, it was projected that the ^{19}F SCS values should be too, and therefore we should be able to work backward and assign the remaining four fluorine shifts for the mono derivative. Indeed, one set of assignments for the remaining four fluorines gave much better agreement than the others, as predicted from SCS values taken from the disubstituted systems. These assignments were therefore used in the calculation of the ^{19}F SCS values for the monotrifluoromethyl OFP system **10** (Table 3).

When these values were used to calculate the shifts for the four bis(trifluoromethyl) derivatives, reasonable agreement was found (Table 4).

Homoannular Substitution. When a second identical substituent is introduced into the *same* ring as the first in an OFP, there are only three possible isomeric products, of which two are meso and one is racemic. The three isomers can in principle be differentiated simply by inspection of the format of the ^{19}F and ^{1}H NMR spectra. The para isomer will result in AB patterns in both the ^{19}F and the ^{1}H spectra, whereas the ortho isomer will produce ^{19}F ABs but singlets in the ^{1}H NMR spectrum. The para meta isomer would also produce no AB patterns in the ^{19}F spectrum but would give an AB in the ^{1}H spectrum. The only isomer to give rise to AB patterns in both fluorine and proton NMR spectra would be the para isomer. This is what was observed for dibromo OFP, **5d**, and bis(trifluoromethyl) OFP, **8b**.

Mass Spectrometry. It has been well documented that mass spectroscopic analysis of [2.2] PCP derivatives provides an excellent method for determination of the number of substituents on each ring.[3,24] This has also been demonstrated to be the case for monosubstituted OFP derivatives,[11] and all the new OFP compounds described herein have mass spectra appropriate to the general rules previously established for both the hydrocarbon and fluorocarbon systems.

This technique provides the simplest way to discriminate between homo- and heteroannular disubstituted isomers. For example, both the para and pseudo-para bis-(trifluoromethyl)-OFP's give the same molecular parent ion of 488. The isomer with a trifluoromethyl group in each ring fragments into two xylylene units of mass 244, whereas the homoannular isomer fragments into unsubstituted and disubstituted xylylene fragments of mass 176 and 312.

Physical Properties. Cram derived many correlations between physical properties and relative orientation of disubstituted [2.2] PCP isomers.[24] These general relationships proved equally valid for the OFP systems and indeed were fundamental to our early characterization work. For example, during column chromatography the disubstituted OFP derivatives always eluted in the same order of pseudo-meta/pseudo-para, pseudo-ortho, pseudo-gem. The pseudo-meta and pseudo-para isomers could never be separated by column chromatography, although they could be separated on a capillary GC (DB5) column. The pseudo-para/pseudo-meta isomer mixture could be enriched in one isomer or the other by fractional crystallization or sublimation, with the pseudo-para isomer being the least soluble and slowest to sublime. In certain cases, analytical samples of pure pseudo-para isomer could be obtained by fractional crystallization. The pseudo-para isomer was also the isomer with the highest melting point.

Characterization Summary. We have demonstrated that both the previously established rules and strategies for characterization of [2.2] PCP and mono OFP derivatives are equally applicable to the identification of disubstituted OFP derivatives and furthermore allow the discrimination between disubstituted OFP isomers. The use of previously derived ^{1}H SCS values allowed the prediction of ^{1}H NMR spectra of disubstituted isomers, and also derived ^{19}F SCS values for trifluoromethyl OFP can be used for the prediction of the ^{19}F NMR shifts of the bridge fluorines for bis(trifluoromethylated) OFP isomers. Mass spectroscopy allows the easiest discrimination between homo- and heteroannular disubstituted isomers.

Conclusions

We report for the first time the synthesis of 27 novel octafluoroparacyclophanes with two substituents on the aromatic rings. Both inter- and intraannular substitution could be controlled by method of functionalization. The characterization of these compounds using a combination of mass spectrometry, ^{19}F and ^{1}H NMR allowed unambiguous determination of the relative locations of the substituents, and these were further confirmed by the general trends and characteristics of their physical properties. Thermal isomerizations were studied, and it was shown that temperatures around 350 °C were required before isomerization through the breaking of difluorobenzyl bonds would occur. This is almost 200 °C higher than required for the analogous hydrocarbon [2.2] PCPs.[22]

We believe this work provides the synthetic and corresponding characterization foundations necessary for a wide variety of future work in the previously barren area of fluorinated cyclophanes.

Experimental Section

All NMR spectra were obtained at ambient temperatures in deuterated acetone, using TMS and $CFCl_3$ as references for ^1H and ^{19}F, respectively. All reagents, unless otherwise specified, were used as purchased from Aldrich or Fischer. Column chromatography was performed using chromatographic silica gel, 200−425 mesh, as purchased from Fischer. Melting points are uncorrected. Mass spectroscopic analyses were performed with an ionizing potential of 70 eV.

Dinitration of OFP 1. Under a counter current of dry nitrogen, nitronium tetrafluoroborate (22.10 g, 166.17 mmol) was added to octafluoroparacyclophane **1** (10.20 g, 28.98 mmol) dissolved in sulfolane (100 mL), and the reaction was warmed to 80 °C and stirred at this temperature overnight. The reaction mixture was then allowed to cool to room temperature and added to ice water (400 mL), and the white precipitate was filtered and chromatographed (hexane/dichloromethane 7/3) to give (R_f = 0.32) pseudo-*m*- and pseudo-*p*-dinitro-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **2a**,**b** (6.92 g, 54% combined; 1:1 mixture): MS *m*/*z* 442 (M^+, 6%), 125 (100). Anal. Calcd for $C_{16}H_6F_8N_2O_4$: C, 43.44; H, 1.36; N, 6.33. Found: C, 43.70; H, 1.23; N, 6.21. **2a:** ^1H NMR δ 8.009 (s, 1H); 8.009 (m, 1H); 7.783 (d, ^3J = 8.10 Hz, 1H); ^{19}F NMR δ −108.806 (d, ^2J = 244.70 Hz, 1F); −111.989 (d, ^2J = 244.70 Hz, 1F); −115.321 (d, ^2J = 239.90 Hz, 1F); −117.317 (d, ^2J = 239.90 Hz, 1F). **2b:** ^1H NMR δ 8.009 (s, 1H); 8.009 (m, 1H); 7.783 (d, ^3J = 8.10 Hz, 1H); ^{19}F NMR δ −109.829 (d, ^2J = 246.95 Hz, 1F); −113.986 (d, ^2J = 246.95 Hz, 1F); −114.352 (d, ^2J = 237.36 Hz, 1F); −115.028 (d, ^2J = 237.36 Hz, 1F); (R_f = 0.20). **Pseudo-*o*-dinitro-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 2c** (3.46 g, 27%): mp 213−215 °C. ^1H NMR δ 8.075 (s, 1H); 7.827 (m, 2H); ^{19}F NMR δ −111.023 (d, ^2J = 244.70 Hz, 1F); −112.293 (d, ^2J = 244,70 Hz, 1F); −114.428 (d, ^2J = 242.44 Hz, 1F); −115.582 (d, ^2J = 242.44 Hz, 1F); MS *m*/*z* 442 (M^+, 10%), 125 (100). Anal. Calcd for $C_{16}H_6F_8N_2O_4$: C, 43.44; H, 1.36; N, 6.33. Found: C, 43.70; H, 1.29; N, 6.19. The combined yield of the three dinitro isomers is 81%.

When only 4 equiv of nitronium tetrafluoroborate was used, the product mixture was subjected to chromatography and shown to contain the mononitrated cyclophane (36%), the pseudo-*m*-**2a** (16%), pseudo-*p*-**2b** (16%) and pseudo-*o*-**2c** (16%) dinitro-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes.

Pseudo-*o*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 3c. A suspension of pseudo-*o*-dinitro-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **2c** (1.30 g, 2.94 mmol) in ethanol/water (1/1 v/v, 50 mL) was stirred for 1 h at room temperature. Iron powder (2.00 g, 35.71 mmol) was added, and the reaction mixture was heated to reflux. Concentrated hydrochloric acid (7 mL) was added dropwise to the mixture, and reflux was continued for 4 h. After this time, the reaction was cooled to room temperature and was added to ice water (200 mL). The solids thus produced were filtered and redissolved in chloroform. This chloroform solution was filtered and evaporated, and the solid residue was chromatographed (chloroform) to give (R_f = 0.41) pseudo-*o*-diamino-1,1,2,2,9,9,-10,10-octafluoro[2.2]paracyclophane **3c** (0.91 g, 82%): mp 211 °C (dec); ^1H NMR δ 6.999 (d, ^3J = 8.40 Hz, 1H); 6.885 (s, 1H); 6.361 (d, ^3J = 8.40 Hz, 1H); ^{19}F NMR δ −106.652 (dd, ^2J = 232.56, ^3J = 9.60 Hz, 1F); −114.370 (d, ^2J = 232.56 Hz, 1F); −106.873 (dd, ^2J = 242.44, ^3J = 9.60 Hz, 1F); −111.223 (d, ^2J = 242.44 Hz, 1F); MS *m*/*z* 382 (M^+, 19%), 191 (100). Anal. Calcd for $C_{16}H_{10}F_8N_2$: C, 50.26; H, 2.62; N, 7.33. Found: C, 50.17; H, 2.41; N, 7.21.

An identical reaction with a 1:1 mixture of pseudo-*m*- and pseudo-*p*-dinitro-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **2a**,**b** gave the corresponding pseudo-meta- and pseudo-para-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **3a**,**b** in 84% yield. (hexane/chloroform 1/1, R_f = 0.46): Anal. Calcd for $C_{16}H_{10}F_8N_2$: C, 50.26; H, 2.62; N, 7.33. Found: C, 49.98; H, 2.55; N, 7.07. MS *m*/*z* 382 (M^+, 21%), 191 (100). **3a:** ^1H NMR δ 7.566 (d, ^3J = 8.40 Hz, 1H); 6.442 (d, ^3J = 8.40 Hz, 1H); 6.084 (s, 1H); ^{19}F NMR δ −100.315 (m, 2F); −112.440 (d, ^2J = 234.25 Hz, 1F); −116.601 (d, ^2J = 234.25 Hz, 1F). **3b:** ^1H NMR δ 7.038 (d, ^3J = 8.40 Hz, 1H); 6.874 (d, ^3J = 8.40 Hz, 1H); 6.003 (s, 1H); ^{19}F NMR δ −103.339 (d, ^2J = 239.33 Hz, 1F); −109.085 (d, ^2J = 239.33 Hz, 1F); −108.562 (d, ^2J = 234.25 Hz, 1F); −109.685 (d, ^2J = 234.25 Hz, 1F).

An ethanol (10 mL) solution containing pseudo-*o*-dinitro-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **2c** (380 mg, 0.86 mmol), cyclohexene (420 mg, 5.16 mmol) and 10% Pd on carbon (0.2 g) was warmed to reflux, and after 15 min of observable reflux, the reaction was evaporated under reduced pressure to a solid residue which was subjected to chromatography (chloroform/hexane 7/3, then chloroform) to give three compounds: (R_f = 0.46) **pseudo-*o*-nitroamino-1,1,2,2,9,9,-10,10-octafluoro[2.2]paracyclophane 6** (40 mg, 11%): ^1H NMR δ 8.267 (s, 1H); 7.692 (d, ^3J = 8.40 Hz, 1H); 7.466 (d, ^3J = 8.40 Hz, 1H); 7.107 (d, ^3J = 8.40 Hz, 1H); 6.631 (d, ^3J = 8.40 Hz, 1H); 6.453 (s, 1H); 5.818 (br s, 2H, NH_2); ^{19}F NMR δ −105.172 (d, ^2J = 244.70 Hz, 1F); −112.620 (d, ^2J = 244.70 Hz, 1F); −106.128 (d, ^2J = 239.90 Hz, 1F); −110.660 (d, ^2J = 239.90 Hz, 1F); −109.339 (d, ^2J = 244.70 Hz, 1F); −112.615 (d, ^2J = 244.70 Hz, 1F); −111.964 (d, ^2J = 234.82 Hz, 1F); −116.298 (d, ^2J = 234.82 Hz, 1F); MS *m*/*z* 412 (M^+, 25%), 191 (100); HRMS calcd for $C_{16}H_8F_8N_2O_2$ 412.0458, found 412.0481. (R_f = 0.20, chloroform) **pseudo-*o*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane 3c** (126 mg, 38%), as above. (R_f = 0.11, chloroform) **pseudo-*o*-hydroxylaminoamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane 7** (51 mg, 15%): ^1H NMR δ 7.609 (s, 1H); 7.118 (d, ^3J = 8.40 Hz, 1H); 6.958 (d, ^3J = 8.40 Hz, 1H); 6.627 (d, ^3J = 8.40 Hz, 1H); 6.373 (d, ^3J = 8.40 Hz, 1H); 6.691 (s, 1H); 8.249 (br s, 1H NH); 7.952 (br s, 1H, OH); 5.337 (br s 2H, NH_2); ^{19}F NMR δ −104.796 (d, ^2J = 242.16 Hz, 1F); −111.062 (d, ^2J = 242.16 Hz, 1F); −106.012 (d, ^2J = 244.70 Hz, 1F); −111.220 (d, ^2J = 244.70 Hz, 1F); −106.120 (d, ^2J = 235.10 Hz, 1F); −113.514 (d, ^2J = 235.10 Hz, 1F); −106.529 (d, ^2J = 232.28 Hz, 1F); −114.462 (d, ^2J = 232.28 Hz, 1F); MS *m*/*z* 398 (M^+, 23%), 207 (5), 191 (100); HRMS calcd for $C_{16}H_{10}F_8ON_2$ 398.0665, found 398.0656.

Typical Diazotization Procedure. A solution of pseudo-*o*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **3c** (2.00 g, 5.24 mmol) in acetic acid (4 mL) was cooled to 0 °C in an ice/brine bath; ice (1.5 mL) and concentrated 98% sulfuric acid (1.5 mL) were carefully added with stirring; and ensuring the temperature was still below 0 °C, sodium nitrite (2.00 g, 28.99 mmol) was added in one batch. The reaction was stirred at this temperature for 2 h and then used for the following transformations:

Pseudo-*o*-dibromo-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 5c. An aqueous solution (10 mL) of copper-(I) bromide (4.00 g, 27.87 mmol) and 47% hydrobromic acid (10 mL) was warmed to 70 °C, and the diazotization solution previously prepared was added in one batch with stirring. The mixture was kept at 70 °C for 1 h and then left to cool overnight. The precipitated product was filtered, and chromatographed (hexane/ether 9/1) to give (R_f = 0.45) pseudo-*o*-dibromo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **5c** (1.60 g, 60%): mp 125−126 °C; ^1H NMR δ 7.845 (s, 1H); 7.520 (d, ^3J = 8.10 Hz, 1H); 7.369 (d, ^3J = 8.10 Hz, 1H); ^{19}F NMR δ −109.460 (d, ^2J = 239.90 Hz, 1F); −113.529 (d, ^2J = 239.90 Hz, 1F); −110.473 (d, ^2J = 239.90 Hz, 1F); −110.620 (d, ^2J = 239.90 Hz, 1F); MS *m*/*z* 510 (M^+, 5%), 508 (2), 512 (2), 254 (100), 256 (94). Anal. Calcd for $C_{16}H_6F_8Br_2$: C, 37.65; H, 1.18. Found: C, 37.69; H, 1.15.

An identical reaction with a 1:1 mixture of pseudo-*m*- and pseudo-*p*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **3a**,**b** gave the corresponding pseudo-*m*- and pseudo-*p*-dibromo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **5a**,**b** in 65% yield: (hexane/chloroform 9/1, R_f = 0.62). Anal. Calcd for $C_{16}H_6F_8Br_2$: C, 37.65; H, 1.18. Found: C, 37.44; H, 1.13. MS *m*/*z* 510 (M^+, 4%), 508 (2), 512 (2), 254 (100), 256 (94). **5a:** ^1H NMR δ 7.428 (s, 1H); 7.799 (d, ^3J = 8.10 Hz, 1H); 7.486 (d, ^3J = 8.40 Hz, 1H); ^{19}F NMR δ −103.640 (d, ^2J = 239.90 Hz,

1F); −113.529 (d, ^2J = 239.90 Hz, 1F); −110.473 (d, ^2J = 239.90 Hz, 1F); −110.620 (d, ^2J = 239.90 Hz, 1F). **5b:** ^{1}H NMR δ 7.165 (s, 1H); 7.895 (d, ^3J = 8.40 Hz, 1H); 7.411 (d, ^3J = 8.40 Hz, 1H); ^{19}F NMR δ −108.141 (d, ^2J = 239.62 Hz, 1F); −109.137 (d, ^2J = 239.62 Hz, 1F); −110.582 (m, 2F).

Pseudo-*o*-diiodo-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 4c. An aqueous solution (10 mL) of potassium iodide (5.11 g, 30.78 mmol) was warmed to 70 °C, and the diazotization solution previously prepared was added in one batch with stirring. The mixture was kept at 70 °C for 1 h and then left to cool overnight. The precipitated product was filtered and chromatographed (hexane/ether 9/1) to give (R_f = 0.42) pseudo-*o*-diiodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **4c** (2.47 g, 78%): mp 132−133 °C; ^{1}H NMR δ 8.157 (s, 1H); 7.457 (d, ^3J = 8.70 Hz, 1H); 7.403 (d, ^3J = 8.70 Hz, 1H); ^{19}F NMR δ −107.330 (d, ^2J = 237.36 Hz, 1F); −112.570 (d, ^2J = 237.36 Hz, 1F); −109.323 (d, ^2J = 239.90 Hz, 1F); −110.319 (d, ^2J = 239.90 Hz, 1F); MS *m*/*z* 604 (M$^+$, 3%), 302 (100). Anal. Calcd for $C_{16}H_6F_8I_2$: C, 31.79; H, 0.99. Found: C, 31.96; H, 0.92.

An identical reaction with a 1:1 mixture of pseudo-*m*- and pseudo-*p*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **3a**,**b** gave the corresponding pseudo-*m*- and pseudo-*p*-diiodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **4a**,**b** in 78% yield: (hexane/ether 9/1, R_f = 0.61). Anal. Calcd for $C_{16}H_6F_8I_2$: C, 31.79; H, 0.99. Found: C, 31.86; H, 0.86. MS *m*/*z* 604 (M$^+$, 3%), 302 (100). **4a:** ^{1}H NMR δ 7.820 (s, 1H); 7.758 (d, ^3J = 8.10 Hz, 1H); 7.450 (d, ^3J = 8.10 Hz, 1H); ^{19}F NMR δ −102.046 (d, ^2J = 241.03 Hz, 1F); −105.807 (d, ^2J = 241.03 Hz, 1F); −115.704 (d, ^2J = 239.90 Hz, 1F); −116.452 (d, ^2J = 239.90 Hz, 1F). **4b:** ^{1}H NMR δ 7.573 (s, 1H); 7.994 (d, ^3J = 8.40 Hz, 1H); 7.482 (d, ^3J = 8.40 Hz, 1H); ^{19}F NMR δ −107.109 (d, ^2J = 237.36 Hz, 1F); −109.445 (d, ^2J = 237.36 Hz, 1F); −108.734 (d, ^2J = 237.36 Hz, 1F); −111.322 (d, ^2J = 237.36 Hz, 1F).

Pseudo-*o*-diphenyl-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 11. Benzene (10 mL) was added to the chilled diazotization solution, and 1 min later an aqueous (3 mL) solution of sodium acetate (1.00 g, 12.20 mmol) was added. The biphasic mixture was allowed to warm to room temperature overnight with vigorous stirring. Ether was then added, and the bright orange organic phase was separated, dried and evaporated. The crude residue was chromatographed (hexane/dichloromethane 9/1) to give (R_f = 0.27) 4-phenyl-1,1,2,2,9,9,-10,10-octafluoro[2.2]paracyclophane **12**[10] (0.72 g, 32%) and (R_f = 0.20) pseudo-*o*-diphenyl-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane **11** (0.42 g, 16%): ^{1}H NMR δ 7.437 (s, 1H); 7.782 (d, ^3J = 8.10 Hz, 1H); 7.641−7.523 (m, 5H); 7.452 (d, ^3J = 8.10 Hz, 1H); ^{19}F NMR δ −104.750 (d, ^2J = 239.62 Hz, 1F); −113.413 (d, ^2J = 239.62 Hz, 1F); −112.688 (d, ^2J = 244.70 Hz, 1F); −117.061 (d, ^2J = 244.70 Hz, 1F); MS *m*/*z* 504 (M$^+$, 8%), 251 (80), 232 (100); HRMS calcd for $C_{28}H_{16}F_8$ 504.1124, found 504.1157.

Pseudo-*o*-bis(trifluoromethyl)-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane 8c. A degassed DMF (40 mL) solution containing pseudo-*o*-diiodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **4c** (3.00 g, 4.97 mmol), methyl 2-(fluorosulfonyl) difluoroacetate (9.53 g, 49.67 mmol) and palladium dichloride (40 mg, 0.23 mmol) was warmed to 80 °C under a blanket of nitrogen. Copper(I) bromide (5.33 g, 37.25 mmol) was added in one portion, and the mixture was maintained at that temperature overnight. Then the mixture was cooled to ambient temperature before adding ice water. The mixture was stirred for 30 min and then the precipitates were removed by filtration and were subjected to column chromatography (hexane/diethyl ether 9/1) affording (R_f = 0.31) **pseudo-*o*-iodotrifluoromethyl-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane 9** (0.27 g 10%): ^{1}H NMR δ 7.309 (s, 1H); 6.726 (s, 1H); 6.892 (d, ^3J = 8.40 Hz, 1H); 6.757 (d, ^3J = 8.40 Hz, 1H); 6.705 (d, ^3J = 8.70 Hz, 1H); 6.652 (d, ^3J = 8.70 Hz, 1H); ^{19}F NMR δ −107.182 (dd, ^2J = 242.16, ^3J = 7.20 Hz, 1F); −112.966 (dq, ^2J = 242.16, ^5J = 29.06 Hz, 1F); −107.635 (dd, ^2J = 239.90, ^3J = 12.10 Hz, 1F); −110.960 (dd, ^2J = 239.90, ^3J = 7.30 Hz, 1F); −108.138 (dd, ^2J = 236.23, ^3J = 12.10 Hz, 1F); −110.315 (dd, ^2J = 236.23, ^3J = 7.30 Hz, 1F); −113.747 (dq, ^2J = 234.82, ^6J = 14.54 Hz, 1F); −114.623 (dd, ^2J = 234.82, ^3J = 7.20 Hz, 1F); −59.257 (dd, ^5J = 29.07, ^6J = 14.54 Hz, 3F); MS *m*/*z* 546 (M$^+$, 5%), 302 (100), 244 (10); HRMS calcd for $C_{17}H_6F_{11}I$ 545.9339, found 545.9401. (R_f = 0.17) **pseudo-*o*-bis(trifluoromethyl)-1,1,2,2,9,9,10,10-octafluoro-[2.2]paracyclophane 8c** (1.65 g, 68%): mp 154−155 °C; ^{1}H NMR δ 7.493 (s, 1H); 7.733 (m, 2H); ^{19}F NMR δ −108.067 (dd, ^2J = 242.16, ^3J = 9.60 Hz, 1F); −112.234 (dq, ^2J = 242.16, ^5J = 29.07 Hz, 1F); −113.163 (dd, ^2J = 237.36, ^3J = 9.60 Hz, 1F); −114.751 (dq, ^2J = 237.36, ^6J = 14.68 Hz, 1F); −59.160 (dd, ^5J = 29.07, ^6J = 14.68 Hz, 3F); MS *m*/*z* 488 (M$^+$, 5%), 244 (100). Anal. Calcd for $C_{18}H_6F_{14}$: C, 44.26; H, 1.24. Found: C, 44.24; H, 1.02.

An identical reaction with a 1:1 mixture of pseudo-*m*- and pseudo-*p*-diiodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **4a**,**b** gave the corresponding pseudo-*m*- and pseudo-*p*-bis(trifluoromethyl)-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophanes **8a**,**b** in 80% yield: (hexane/ether 9/1, R_f = 0.67). Anal. Calcd for $C_{18}H_6F_{14}$: C, 44.26; H, 1.24. Found: C, 44.32; H, 1.15. MS *m*/*z* 488 (M$^+$, 4%), 244 (100).

There was no evidence of any iodo-trifluoromethyl isomers in this reaction. (It was possible to collect an analytic sample of the more insoluble pseudo-*p*-bis(trifluoromethyl)-1,1,2,2,9,9,-10,10-octafluoro[2.2]paracyclophane **8b** by fractional crystallization, which had mp 199−200 °C). **8a:** ^{1}H NMR δ 7.824 (s, 1H); 7.710 (d, ^3J = 8.40 Hz, 1H); 7.543 (d, ^3J = 8.40 Hz, 1H); ^{19}F NMR δ −105.860 (dq, ^2J = 242.16, ^6J = 14.68 Hz, 1F); −112.029 (dq, ^2J = 242.16, ^5J = 29.07 Hz, 1F); −113.562 (d, ^2J = 247.24 Hz, 1F); −118.289 (d, ^2J = 247.24 Hz, 1F); −58.633 (dd, ^5J = 29.07, ^6J = 14.68 Hz, 3F). **8b:** ^{1}H NMR δ 7.850 (s, 1H); 7.693 (d, ^3J = 8.40 Hz, 1H); 7.574 (d, ^3J = 8.40 Hz, 1H); ^{19}F NMR δ −107.280 (dd, ^2J = 242.16, ^3J = 7.06 Hz, 1F); −112.902 (dq, ^2J = 242.16, ^5J = 31.61 Hz, 1F); −111.769 (dq, ^2J = 237.36, ^6J = 9.88 Hz, 1F); −115.648 (dd, ^2J = 237.36, ^3J = 7.06 Hz, 1F); −58.300 (dd, ^5J = 31.61, ^6J = 9.88 Hz, 3F).

4-Trifluoromethyl-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 10. An acetic acid solution (30 mL) containing pseudo-*o*-iodo-trifluoromethyl-1,1,2,2,9,9,10,10-octafluoro-[2.2]paracyclophane **9** (230 mg, 0.42 mmol) and zinc (110 mg, 1.70 mmol) was refluxed overnight. The mixture was cooled to ambient temperatures and added to ice water (100 mL). The precipitates were collected and subjected to column chromatography (hexane/diethyl ether 8/2) producing (R_f = 0.56) 4-trifluoromethyl-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **10** (160 mg, 91%), analytically identical to an authentic sample.[11]

Pseudo-*o*-diacetamido-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane, 14c. A dichloromethane (5 mL) solution of pseudo-*o*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **3c** (200 mg, 0.52 mmol) was warmed to reflux, acetyl chloride (2 mL) was added dropwise, and the reaction was refluxed overnight. Rotary evaporation afforded a pale brown residue, which after chromatography (hexane/ether 1/9) gave (R_f = 0.60) pseudo-*o*-diacetamido-1,1,2,2,9,9,10,10-octafluoro-[2.2]paracyclophane **14c** (0.24 g, 97%): mp 199−201 °C; ^{1}H NMR δ 7.818 (s, 1H); 7.392 (d, ^3J = 8.10 Hz, 1H); 7.074 (d, ^3J = 8.40 Hz, 1H); 8.854 (br s, 1H, NH); 2.243 (s, 3H, CH_3); ^{19}F NMR δ −107.595 (d, ^2J = 244.70 Hz, 1F); −111.870 (d, ^2J = 244.70 Hz, 1F); −111.439 (d, ^2J = 237.36 Hz, 1F); −114.882 (d, ^2J = 237.36 Hz, 1F); MS *m*/*z* 466 (M$^+$, 27%), 446 (40), 233 (12), 191 (100). Anal. Calcd for $C_{20}H_{14}F_8N_2O_2$: C, 51.50; H, 3.00; N, 6.01. Found: C, 51.32; H, 3.05; N, 5.91.

An identical reaction with a 1:1 mixture of pseudo-*m*- and pseudo-*p*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **3a**,**b** gave the corresponding pseudo-*m*- and pseudo-*p*-diacetamido-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes, **14a** and **b**, in 84% yield: (hexane/ether 4/6, R_f = 0.44). Anal. Calcd for $C_{20}H_{14}F_8N_2O_2$: C, 51.50; H, 3.00; N, 6.01. Found: C, 51.38; H, 2.91; N, 5.91. MS *m*/*z* 466 (M$^+$, 5%), 446 (42), 233 (22), 191 (100). Pseudo-meta isomer **14a**: ^{1}H NMR δ 8.112 (s, 1H); 7.401 (d, ^3J = 8.40 Hz, 1H); 7.013 (d, ^3J = 8.40 Hz, 1H); 8.817 (br s, 1H, NH); 2.251 (s, 3H, CH_3); ^{19}F NMR δ −103.130 (d, ^2J = 247.10 Hz, 1F); −104.959 (d, ^2J = 247.10 Hz, 1F); −115.615 (d, ^2J = 237.36 Hz, 1F); −115.911 (d, ^2J = 237.36 Hz, 1F). Pseudo-para isomer **14b**: ^{1}H NMR δ 7.808 (s,

1H); 7.401 (d, ^3J = 8.10 Hz, 1H); 7.082 (d, ^3J = 8.10 Hz, 1H); 8.942 (br s, 1H, NH); 2.251 (s, 3H, CH_3); ^{19}F NMR δ −107.616 (d, ^2J = 244.70 Hz, 1F); −111.836 (d, ^2J = 244.70 Hz, 1F); −113.462 (d, ^2J = 237.36 Hz, 1F); −114.314 (d, ^2J = 237.36 Hz, 1F).

Pseudo-*o*-bis(trifluoroacetamido)-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane 13c. A solution of pseudo-*o*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **3c** (270 mg, 0.71 mmol) in trifluoroacetic anhydride (4 mL) was refluxed overnight. After this time, rotary evaporation yielded a solid residue that after chromatography (chloroform) afforded (R_f = 0.64) pseudo-*o*-bis(trifluoroacetamido)-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **13c** (0.39 g, 95%): mp 123−124 °C; ^{1}H NMR δ 7.550 (s, 1H); 7.470 (d, ^3J = 8.40 Hz, 1H); 7.237 (d, ^3J = 8.40 Hz, 1H); 9.801 (br s, 1H, NH); ^{19}F NMR δ −109.464 (d, ^2J = 247.24, Hz, 1F); −112.265 (d, ^2J = 247.24, Hz, 1F); −113.333 (d, ^2J = 239.90 Hz, 1F); −114.249 (d, ^2J = 239.90, Hz, 1F); −75.832 (s, 3F); MS *m*/*z* 574 (M^+, 6%), 554 (32), 287 (22), 267 (100). Anal. Calcd for $C_{20}H_8F_{14}N_2O_2$: C, 41.81; H, 1.39; N, 4.88. Found: C, 41.64; H, 1.29; N, 4.80.

An identical reaction with a 1:1 mixture of pseudo-*m*- and pseudo-*p*-diamino-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes **3a**,**b** gave the corresponding pseudo-*m*- and pseudo-*p*-bis(trifluoroacetamido)-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophanes **13a** and **b** in 97% yield: (hexane/ether 4/6, R_f = 0.44). Anal. Calcd for $C_{20}H_8F_{14}N_2O_2$: C, 41.81; H, 1.39; N, 4.88. Found: C, 41.77; H, 1.34; N, 4.81. MS *m*/*z* 574 (M^+, 3%), 554 (32), 287 (82), 267 (100). Pseudo-meta isomer **13a**: ^{1}H NMR δ 7.641 (s, 1H); 7.533 (d, ^3J = 8.40 Hz, 1H); 7.252 (d, ^3J = 8.40 Hz, 1H); 10.117 (br s, 1H, NH); ^{19}F NMR δ −107.988 (d, ^2J = 247.24 Hz, 1F); −108.255 (d, ^2J = 247.24 Hz, 1F); −116.278 (d, ^2J = 239.90 Hz, 1F); −118.013 (d, ^2J = 239.90 Hz, 1F); −75.514 (s, 3F). Pseudo-para isomer **13b**: ^{1}H NMR δ 7.765 (s, 1H); 7.406 (d, ^3J = 8.40 Hz, 1H); 7.374 (d, ^3J = 8.40 Hz, 1H); 10.117 (br s, 1H, NH); ^{19}F NMR δ −111.130 (d, ^2J = 246.95 Hz, 1F); −111.292 (d, ^2J = 246.95 Hz, 1F); −113.375 (d, ^2J = 239.62 Hz, 1F); −115.955 (d, ^2J = 239.62 Hz, 1F); −75.574 (s, 3F).

Pseudo-*o*-diphenyl-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 11. A degassed THF solution (5 mL) containing pseudo-*o*-diiodo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **4c** (300 mg, 0.50 mmol) and palladium dichloride (21 mg, 0.12 mmol) was stirred and brought to reflux under a nitrogen atmosphere. A 1 M THF solution of phenylmagnesium bromide (3.0 mL, 3.00 mmol) was added via syringe, and the black solution was refluxed overnight. Evaporation of the solvent was followed by the addition of ice water, and the precipitated solids were chromatographed (hexane/dichloromethane 9/1) to give (R_f = 0.44) 4-phenyl-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **12**[11] (43 mg, 20%) and (R_f = 0.37) pseudo-*o*-diphenyl-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **11** (53 mg, 21%): ^{1}H NMR δ 7.437 (s, 1H); 7.782 (d, ^3J = 8.10 Hz, 1H); 7.641−7.523 (m, 5H); 7.452 (d, ^3J = 8.10 Hz, 1H); ^{19}F NMR δ −104.750 (d, ^2J = 239.62 Hz, 1F); −113.413 (d, ^2J = 239.62 Hz, 1F); −112.688 (d, ^2J = 244.70 Hz, 1F); −117.061 (d, ^2J = 244.70 Hz, 1F); MS *m*/*z* 504 (M^+, 8%), 251 (80), 232 (100); HRMS calcd for $C_{28}H_{16}F_8$ 504.1124, found 504.1157.

***p*-Dibromo-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 5d.** A trifluoroacetic acid solution (3 mL) containing 1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **1** (1.00 g, 2.84 mmol) and *N*-bromosuccinimide (2.02 g, 11.35 mmol) was stirred magnetically in a flask protected by a silica drying tube. After 5 min, 98% sulfuric acid (1 mL) was added, and left to stir for 16 h. After this time analysis by ^{19}F NMR and TLC showed the presence of starting material, mono-bromo OFP and several dibromide isomers, one of which seemed predominant. The reaction was warmed to 80 °C and left another 12 h. The mixture was cooled to ambient temperatures, and added to 100 mL of ice water. The pale yellow precipitate was subjected to column chromatography (hexane/chloroform 50/1) and gave (R_f = 0.36) *p*-dibromo-1,1,2,2,9,9,-10,10-octafluoro[2.2]paracyclophane **5d** (0.65 g, 55%): mp 159−161 °C; ^{1}H NMR δ 7.416 (s, 1H); 7.970 (d, ^3J = 8.40 Hz, 1H); 7.481 (d, ^3J = 8.40 Hz, 1H); ^{19}F NMR δ −110.194 (d, ^2J = 237.36 Hz, 1F); −112.642 (d, ^2J = 237.36 Hz, 1F); −111.499 (m, 2F); MS *m*/*z* 508 (M^+, 6%), 510 (13), 512 (6), 334 (5), 254 (53), 256 (49), 176 (100). Anal. Calcd for $C_{16}H_6F_8Br_2$: C, 37.65; H, 1.18. Found: C, 37.81; H, 1.19. (R_f = 0.20) A mixture of monobromo-, dibromo- (2 isomers) and tribromo-(3 isomers) −1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes (0.172 g). GLCMS indicted that the dibromo isomers in the second fraction showed one isomer each of hetero- and homoannular distribution, while the tribromides all contained two bromines on one ring and one in the other. This second fraction was not further analyzed.

***p*-Bis(trifluoromethyl)-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane 8d.** A degassed DMF (20 mL) solution containing *p*-dibromo-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane **5d** (0.53 g, 1.04 mmol) and methyl 2-(fluorosulfonyl) difluoroacetate (0.80 g, 4.16 mmol) was warmed to 100 °C under a blanket of nitrogen. Copper(I) bromide (0.59 g, 4.16 mmol) was added in one portion, and the mixture was maintained at that temperature overnight. Then the mixture was cooled to ambient temperature before adding ice water. The mixture was stirred for 30 min and then the precipitates were removed by filtration and were subjected to column chromatography (hexane/diethyl ether 9/1) affording (R_f = 0.72) *p*-bis(trifluoromethyl)-1,1,2,2,9,9,10,10-octafluoro[2.2]-paracyclophane **8d** (66 mg, 13%): mp 125−126 °C; ^{1}H NMR δ 7.810 (s, 1H); 7.427 (m, 2H); ^{19}F NMR δ −109.271 (dd, ^2J = 244.67, ^3J = 9.88 Hz, 1F); −112.848 (dq, ^2J = 244.67, ^5J = 29.07 Hz, 1F); −113.468 (dd, ^2J = 232.54, ^3J = 9.88 Hz, 1F); −114.830 (dq, ^2J = 232.54, ^6J = 16.93 Hz, 1F); −59.187 (dd, ^5J = 29.07, ^6J = 16.93 Hz, 3F); MS *m*/*z* 488 (M^+, 3%), 312 (3), 176 (100). Anal. Calcd for $C_{18}H_6F_{14}$: C, 44.26; H, 1.23. Found: C, 44.47; H, 1.19. (R_f = 0.40) 4-Trifluoromethyl-1,1,2,2,9,9,-10,10-octafluoro[2.2]paracyclophane **10** (74 mg, 17%), whose characterization was identical to an authentic sample.[11]

Thermal Isomerization. A tube containing pseudo-*o*-bis-(trifluoroacetamido)-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophane, **13c**, (90 mg, mmol) was evacuated, sealed and immersed in a Woods metal heating bath at 381−390 °C for 2 h. After this time, the tube was cooled, opened and shown by ^{19}F NMR to contain both pseudo-*o*- and pseudo-*p*-bis(trifluoroacetamido)-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes in a 5:1 ratio. This material was placed into another identical tube, and again evacuated, sealed and immersed into the Woods metal heating bath and heated at 350−363 °C for 24 h. The resulting product mixture was shown by ^{19}F NMR to now contain a 1:7 ratio of pseudo-*o*- and pseudo-*p*-bis(trifluoroacetamido)-1,1,2,2,9,9,10,10-octafluoro[2.2]paracyclophanes. Integration versus an internal standard of trifluorotoluene showed the mass balance of the two isomers was 75%.

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